

## A Treatment For Beta-thalassemia via High-Efficiency Targeted Genome Editing of Hematopoietic Stem Cells

### Grant Award Details

A Treatment For Beta-thalassemia via High-Efficiency Targeted Genome Editing of Hematopoietic Stem Cells

**Grant Type:** Strategic Partnership II

**Grant Number:** SP2-06902

**Project Objective:** Objective of the study is to develop an autologous stem cell gene therapy for Beta Thalassemia. Team developed a zinc-finger nuclease genome editing strategy for beta-Thalassemia designed to specifically knock out the gene encoding the BCL 11A transcription factor. Objective of the study included completion of the IND-enabling studies, filing of an IND and conduct of a Phase 1 clinical trial.

**Investigator:**

<b>Name:</b>	Fyodor Urnov
<b>Institution:</b>	Sangamo BioSciences, Inc.
<b>Type:</b>	PI

**Disease Focus:** Blood Disorders, Pediatrics

**Human Stem Cell Use:** Adult Stem Cell

**Award Value:** \$2,760,540

**Status:** Closed

### Progress Reports

**Reporting Period:** Year 1

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### Grant Application Details

**Application Title:** A Treatment For Beta-thalassemia via High-Efficiency Targeted Genome Editing of Hematopoietic Stem Cells

**Public Abstract:**

$\beta$ -thalassemia is a genetic disease caused by diverse mutations of the  $\beta$ -globin gene that lead to profoundly reduced red blood cell (RBC) development. The unmet medical need in transfusion-dependent  $\beta$ -thalassemia is significant, with life expectancy of only ~30-50 years despite standard of care treatment of chronic blood transfusions and iron chelation therapy. Cardiomyopathy due to iron overload is the major cause of mortality, but iron-overload induced multiorgan dysfunction, blood-borne infections, and other disease complications impose a significant physical, psychosocial and economic impact on patients and families. An allogeneic bone marrow transplant (BMT) is curative. However, this therapy is limited due to the scarcity of HLA-matched related donors (<20%) combined with the significant risk of graft-versus-host disease (GvHD) after successful transplantation of allogeneic cells.

During infancy, gamma-globin-containing fetal hemoglobin protects  $\beta$ -thalassemia patients from developing disease symptoms until gamma globin is replaced by adult-type  $\beta$ -globin chains. The proposed therapeutic intervention combines the benefits of re-activating the gamma globin gene with the curative potential of BMT, but without the toxicities associated with acute and chronic immunosuppression and GvHD. We hypothesize that harvesting hematopoietic stem and progenitor cells (HSPCs) from a patient with  $\beta$ -thalassemia, using genome editing to permanently re-activate the gamma globin gene, and returning these edited HSPCs to the patient could provide transfusion independence or greatly reduce the need for chronic blood transfusions, thus decreasing the morbidity and mortality associated with iron overload. The use of a patient's own cells avoids the need for acute and chronic immunosuppression, as there would be no risk of GvHD. Moreover, due to the self-renewing capacity of HSPCs, we anticipate a lifelong correction of this severe monogenic disease.

**Statement of Benefit to California:**

Our proposed treatment for transfusion dependent  $\beta$ -thalassemia will benefit patients in the state by offering them a significant improvement over current standard of care.  $\beta$ -thalassemia is a genetic disease caused by diverse mutations of the  $\beta$ -globin gene that lead to profoundly reduced red blood cell (RBC) development and survival resulting in the need for chronic lifelong blood transfusions, iron chelation therapy, and important pathological sequelae (e.g., endocrinopathies, cardiomyopathies, multiorgan dysfunction, bloodborne infections, and psychosocial/economic impact). Incidence is estimated at 1 in 100,000 in the US, but is more common in the state of California (incidence estimated at 1 in 55,000 births) due to immigration patterns within the State. While there are estimated to be about 1,000-2,000  $\beta$ -thalassemia patients in the US, one of our proposed clinical trial sites has the largest thalassemia program in the Western United States, with a population approaching 300 patients. Thus, the state of California stands to benefit disproportionately compared to other states from our proposed treatment for transfusion dependent  $\beta$ -thalassemia.

An allogeneic bone marrow transplant (BMT) is curative for  $\beta$ -thalassemia, but limited by the scarcity of HLA-matched related donors (<20%) combined with the significant risk of graft-versus-host disease (GvHD) after successful transplantation of allogeneic cells. Our approach is to genetically engineer the patient's own stem cells and thus (i) solve the logistical challenge of finding an appropriate donor, as the patient now becomes his/her own donor; and (ii) make use of autologous cells abrogating the risk of GvHD and need for acute and chronic immunosuppression.

Our approach offers a compelling pharmacoeconomic benefit to the State of California and its citizens. A lifetime of chronic blood transfusions and iron chelation therapy leads to a significant cost burden; despite this, the prognosis for a transfusion dependent  $\beta$ -thalassemia patient is still dire, with life expectancy of only ~30-50 years. Our proposed one-time treatment aims to reduce or eliminate the need for costly chronic blood transfusions and iron chelation therapy, while potentially improving the clinical benefit to patients, including the morbidity and mortality associated with transfusion-induced iron overload.

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